Management of meconium aspiration syndrome

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Abstract
Meconium aspiration syndrome (MAS) affects 0.43–2.1 in 1000 live births and can be life-threatening. A variety of treatment strategies is used, many of which do not have a solid evidence base to support them, but do appear to be effective. Routine suction of the fetal pharynx prior to delivery of the shoulders is not effective in reducing the incidence of MAS and neither is routine suction of the trachea after birth in vigorous infants. Tracheal suction after birth is still recommended for infants who are not vigorous. After delivery close attention must be paid to the management of the respiratory status of these infants. Some will require ventilation, and surfactant, inhaled nitric oxide and high frequency oscillatory ventilation may all be of benefit in some cases. For the most severely affected, extracorporeal life support has been shown to be effective in reducing the mortality of this condition.

Keywords extracorporeal membrane oxygenation; high frequency ventilation; infant; labour, induced; meconium aspiration syndrome; newborn; nitric oxide; persistent fetal circulation syndrome; pulmonary surfactant

Introduction
Meconium aspiration syndrome (MAS) remains one of the most challenging conditions faced by neonatologists. There is no universal definition, but it is generally accepted that MAS is present when there is respiratory distress associated with the passage of meconium before birth, with characteristic radiological changes (Figure 1) and without an alternative aetiology for the respiratory symptoms. In the developed world, 0.43–2.1 in 1000 live births require mechanical ventilation for MAS, the majority being term or post term. A recent study showed a mortality of 2.5%, representing 0.96 in 100,000 live births.

Meconium staining of the amniotic fluid (MSAF) is observed in 4.3% of deliveries before 37 weeks’ gestation, increasing with advancing gestation beyond 37 weeks to be present in approximately 12% of all deliveries. In most of these cases, the passage of meconium is not associated with any demonstrable adverse fetal conditions and probably reflects developing fetal gut maturity.

However, the fetus also passes meconium in response to stress, such as hypoxia–ischaemia. The commonly accepted model of the pathogenesis of MAS is that meconium is passed in utero in response to stress such as hypoxia–ischaemia. The stress also provokes reflex fetal gasping, which causes meconium to be aspirated into the fetal upper airway. The meconium is then able to enter the distal airways. The extent to which the meconium enters the distal airways before delivery or after delivery with the onset of breathing is unclear and remains a source of controversy in deciding the appropriate airway management at birth. The four main pulmonary characteristics of MAS are mechanical airway obstruction, chemical pneumonitis, surfactant inhibition and pulmonary vasoconstriction. These features reflect both the direct effects of meconium in the airways and the prenatal hypoxic-ischaemic insult that is often associated. Typically, respiratory signs of tachypnoea, cyanosis and chest hyperinflation are present from soon after birth, though in a proportion of cases they develop over some hours after delivery.

Management
General supportive measures
Most babies born through meconium-stained liquor do not require any resuscitation at birth and remain well. Infants with MSAF who are born in good condition, are free of respiratory distress and have no other perinatal risk factors should receive routine postnatal care. Those who develop respiratory distress require further management, with admission to a neonatal unit. There are little objective data on the optimal general management of babies developing MAS, but standard monitoring and treatment should generally include:

- close observation and monitoring of oxygen saturation, heart rate and respiratory rate
- avoidance of excessive handling
- use of intravenous fluids until the respiratory difficulty diminishes

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• monitoring of blood glucose as the infant may be at increased risk of hypoglycaemia after a hypoxic-ischaemic insult
• use of oxygen therapy to maintain saturation in the upper 90s in order to minimize pulmonary hypertension
• monitoring of pCO2 to detect worsening respiratory acidosis.

It is usual practice to give any newborn with respiratory symptoms antibiotics pending the results of blood cultures, even though in the majority of cases cultures are eventually negative. As meconium is sterile, there is no specific rationale for the use of antibiotics in the treatment of MAS, more a general concern that the meconium may not be the cause of the infant’s symptoms or that infection triggered the stress response and passage of meconium. Studies have shown that in those without predisposing risk factors for infection, antibiotics do not appear to influence the outcome of MAS.7 Before abandoning antibiotic treatment, however, it should be borne in mind that, although sepsis is relatively infrequent, it is potentially devastating, so studies with large numbers of cases will be needed before it can be concluded reliably that antibiotics should not routinely be given.

Current practice for the management of MAS can be divided into perinatal and postnatal management.

Perinatal management

Management of the ‘post dates’ pregnancy: there is a clear association between advancing gestation and the incidence of MAS, particularly beyond 40 weeks’ gestation. This may partly explain the variations in incidence of MAS as management of ‘post dates’ delivery varies.3 MAS is reduced after induction of labour post dates in comparison with expectant management.8 The relative risk of MAS after induction versus expectant management is 0.29 (95% CI 0.12–0.68) at 41 weeks and 0.66 (95% CI 0.24–1.81) at 42 weeks (not significant). However, the absolute risk is small and this in isolation is not considered an indication for induction of labour beyond term.

Amnioinfusion: the infusion of fluid transcervically during a labour complicated by meconium-stained liquor has been considered to be of possible benefit in reducing MAS, either by diluting thick meconium or by providing support to the umbilical cord and so reducing the risk of hypoxia–ischaemia due to cord obstruction. In a systematic review of published studies, Xu et al. concluded that the practice may be of benefit in settings where close electronic intrapartum monitoring is not available, but does not prevent MAS in settings where close monitoring could be achieved.9 These findings have been questioned, with discussion around the inclusion of trials in the analysis,10 but the practice of amnioinfusion has not been widely adopted.

Pharyngeal suction before delivery of the shoulders: until recently it was common practice to recommend intrapartum suctioning of the fetal oropharynx at the maternal perineum, before delivery of the fetal shoulders, with the aim of removing meconium from the upper airway before the onset of breathing. A large multicentre randomized trial has shown that this is not effective in reducing the incidence of MAS,11 the need for mechanical ventilation or the risk of mortality. This practice is no longer recommended in neonatal resuscitation guidelines.12,13 Other practices aimed at promoting effective upper airway suction, such as chest splinting to prevent breathing before suction has been carried out, have not been studied properly and are not recommended.

Postpartum management

Tracheal suction: there is still some uncertainty about the value of attempting to suction meconium directly from the trachea. The practice of suctioning the trachea immediately after birth was previously believed to reduce the incidence of MAS.14 However, another large multicentre trial has shown that in vigorous infants (defined as having a heart rate more than 100 beats/min, as well as presence of spontaneous respirations and reasonable tone), there is no benefit from routine suction of the trachea.15 It is still recommended that infants who are not vigorous at delivery undergo laryngoscopy and tracheal suction before the use of positive pressure ventilation,12 but the value of this practice has not been established with a definitive randomized study.

Nasal continuous positive airway pressure (nCPAP) is often used as an intermediate level of support in infants with impaired respiratory function. Although its use has been described in MAS,1,7,16 it has not been studied systematically and shown to be of benefit. As MAS is associated with gas trapping and air leaks due to airway obstruction, some would consider nCPAP to be contraindicated. The use of nCPAP in MAS should be considered experimental until better evidence defines whether it has a role.

Ventilation: Conventional – ventilating infants with MAS can be difficult and the indications for commencing ventilation are not established. As there can be different disease patterns, with some infants having very patchy disease and others a more homogenous problem, no single approach to ventilation is optimal. The most commonly described pattern is to use a low level of positive end expiratory pressure (PEEP) and a long expiratory time, to avoid worsening any gas trapping,17 though this approach may well need to be adapted depending on the response of the infant. Pulmonary flow graphics can be of use in tailoring the expiratory time to the mechanics of a particular infant’s lungs to ensure that expiration is complete.

Infants with MAS are often severely ill, with a requirement for a high FiO2 and airway pressures, and it is common for both sedation and paralysis to be used to optimize infant–ventilator interaction.

High frequency oscillatory ventilation (HFOV) – because the disease can be severe and high pressures are often required when conventional ventilation is used, HFOV is also a commonly used mode.1,16,18 Again, the role of HFOV in MAS has not been defined through good quality trials, though in a sub-group of a larger trial,19 the use of HFOV lead to short-term improvements in gas exchange.

Surfactant: Replacement – meconium is a potent inhibitor of surfactant function.20 Clinical trials have not demonstrated a reduction in mortality with the use of surfactant replacement, but in a meta-analysis of two trials which enrolled 208 infants,21 the need for extracorporeal life support (ECLS) was significantly reduced (RR 0.64, 95% CI 0.46–0.91; NNT 6, 95% CI 3–25). The mortality of infants with MAS when treated with ECLS is now so low that it is unlikely that controlled trials of surfactant therapy in this condition could use mortality as an outcome. Most would now consider
Surfactant treatment to be an integral part of the treatment of MAS. The response to a single dose of surfactant can be blunt and several doses can be required before the desired response is seen. It is not uncommon for treatment to be followed by a mild deterioration in condition for a few minutes, with reduced saturations and a mild increase in pCO₂, but this is usually short lived.

**Lavage** – an alternative to surfactant replacement therapy is to use lavage with relatively large volumes of diluted surfactant to facilitate removal of meconium from the lungs, whilst maintaining sufficient surfactant function. This technique has shown promise in small preliminary studies but some infants do not tolerate it well. Experimental work is ongoing to establish the most effective treatment schedules and preparations. Larger clinical trials will be required to establish the place of this treatment. Given the evidence from controlled trials for the efficacy of conventional surfactant therapy in MAS, lavage should probably not be compared to no surfactant treatment in future trials.

**Nitric oxide**: many infants with MAS have a degree of persistent pulmonary hypertension of the newborn (PPHN) and consequently have disproportionate difficulty with oxygenation in relation to their apparent degree of lung disease. Close attention to basic homeostasis, including maintenance of a generous systemic blood pressure, control of acidosis and avoidance of hypercarbia, should help to minimize this problem. Inhaled nitric oxide (iNO) has emerged as the treatment of choice for PPHN in term or near-term infants due to its efficacy in reducing the number of infants who go on to require ECLS and its relatively selective action on the pulmonary vasculature. As iNO is delivered as an inhaled gas, good alveolar recruitment is required to maximize its effectiveness and it may be more effective in combination with HFOV if the lung disease is severe. As a sub-group within larger studies of iNO in term and near-term infants with severe respiratory failure and or PPHN, infants with MAS represent a large proportion of the infants studied but they have not been studied in isolation or reported separately in sufficient numbers to enable definitive conclusions about the relative efficacy of iNO in MAS. A review did not show any reduction in mortality with the use of iNO, but did demonstrate a reduction in the need for ECLS, a technique discussed below. Avoidance of the need for this invasive and not universally available technique is viewed as a benefit of iNO therapy, so it has been widely adopted in the treatment of MAS-related PPHN.

**Corticosteroids**: meconium produces a chemical pneumonitis as a major part of MAS. Despite this, a Cochrane review of two small studies of corticosteroids in MAS showed no benefit from steroid therapy. Infants treated with steroids remained oxygen dependent for longer. A further two small studies have since contradicted this finding. Infants treated with steroids showed a reduction in the duration of oxygen dependence and improved X-ray appearances. Further studies are required and, with the concerns that have arisen from the use of steroids to treat bronchopulmonary dysplasia about the possible effects of high dose steroids on infant growth and development, speculative treatment should best be avoided in the interim. Given the complexity and expense of some of the other treatment modalities, it would be helpful to determine more reliably whether steroids have any role, particularly in settings where resources are more limited.

**Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS)**: the effects of MAS on the lung are mostly reversible, so it is an ideal candidate disease for rescue therapy with ECLS in severe cases. The mortality of severe MAS was reduced by ECLS treatment in the UK collaborative ECMO trial and outcome data from ECLS registries indicate that the mortality rate of infants with MAS who are treated with ECLS is extremely low. Despite this, the use of ECLS in MAS has fallen over time, a decline that may be attributable to increased use of HFOV, iNO and surfactant. This trend has meant that the population of infants receiving ECLS for MAS are at the sicker end of the disease spectrum, and potentially at greater risk of an adverse outcome. There is concern that ECLS should be being used earlier, particularly as newer ECLS techniques have reduced complication rates. A call has been made for more relaxed entry criteria for ECLS in MAS. It is very important to ensure that infants who have or are developing severe disease are discussed with an ECLS centre early so that the timing of transfer can be optimized and the risk of death prior to ECLS can be minimized.

**Outcome**

MAS produces intense lung inflammation and gives rise to the need for potentially damaging and toxic therapies. Although most infants who survive recover to good health, there are longer term effects on pulmonary function. This has been studied by looking at functional and objective measures, and an increased frequency of respiratory symptoms and abnormal pulmonary function testing has been found.

As MAS is closely associated with perinatal hypoxia-ischaemia, there is an accompanying risk of adverse neurological outcome, which will no doubt be compounded by postnatal cardiorespiratory compromise and exposure to therapies which in themselves may increase the risk of adverse outcome.

**Conclusions**

As with much in neonatal medicine, the management of MAS has evolved over time, resulting in a group of treatment strategies being used that are seen individually to be effective, but have not been subjected to adequate clinical study to determine their optimal place in the therapy of the condition. Considerable challenges remain in improving the outcome from this condition, both in its prevention and management, which should be achieved through well-designed clinical trials.

**REFERENCES**


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**Practice points**

- **MAS occurs more commonly in post dates pregnancies and is reduced when labour is induced, in comparison with continued expectant management**
- **The role of amniinofusion is uncertain**
- **Routine suction of the pharynx at delivery and of the trachea in vigorous infants does not reduce the incidence of MAS. It is still recommended that non-vigorous infants have tracheal suction performed before positive pressure ventilation is given**
- **In ventilated infants with severe hypoxaemic respiratory failure, surfactant replacement, high frequency oscillatory ventilation and inhaled nitric oxide are effective strategies**
- **Extracorporeal life support (ECLS) has been shown to reduce mortality in the most severely affected infants**
- **In infants with significant disease, early discussion with an ECLS centre should be considered**